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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/394,006	09/10/99	BERGER D	P-4762

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RICHARD J RODRICK ESQ
BECTON DICKINSON AND COMPANY
1 BECTON DRIVE
FRANKLIN LAKES NJ 07417

EXAMINER	
FORMAN, B	
ART UNIT	**PAPER NUMBER**
1655	15

DATE MAILED: 08/17/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/394,006	BERGER ET AL.	
	Examiner	Art Unit	
	BJ Forman	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-8,10 and 12-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-8,10 and 12-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to papers filed 20 June 2001 in Paper No. 14 in which claim 1 was amended. All of the amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action of Paper No. 13 dated 22 March 2001 under 35 U.S.C. 112, first paragraph are maintained. The previous rejections under 35 U.S.C. 103 are withdrawn in view of the amendments and new ground for rejection. All of the arguments have been thoroughly reviewed and are discussed below.

Currently claims 1-4, 6-8, 10 and 12-17 are under prosecution.

Specification

2. The spacing of the lines of the specification is such as to make reading and entry of amendments difficult. New application papers with lines double spaced on good quality paper are required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

First paragraph of 35 U.S.C. 112: New Matter

4. Claims 1-4, 6-8, 10 and 12-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims as amended are drawn to compositions comprising of a first substance capable of precipitating or denaturing

proteins whose concentration is less than 80% of the total composition and a second facilitator substance to aid in the infusion of the first substance whose concentration is greater than 20% of the total composition wherein the concentrations of the first and second substances are effective to stabilize the nucleic acids of said at least one cell in a specimen and wherein the combined concentration of said first and second substances is 100% of the composition. The claimed compositions encompass a very large genus of compositions not disclosed in the specification i.e. the claims are drawn to a first substance having a large genus of concentrations ranging from 0.001% to 79.99% and a second substance having a large genus of concentrations ranging from 20.001% to 99.99%. The specification teaches the preferred embodiment is 50% methanol/50% DMSO (page 4, lines 19-24). Additionally, the specification teaches 8 additional compositions consisting of 80% methanol/20% DMSO; 40% methanol + 40% ethanol/ 20% DMSO; 25% methanol + 25% ethanol/ 50% DMSO; and 80% ethanol/20%DMSO; 20% methanol/80% DMSO; 40% methanol/60% DMSO; 60% methanol/40% DMSO; 100% methanol; and 100%DMSO (Examples 4-12, pages 14-19, 21 & 23). While the specification teaches 9 compositions, the specification does not teach the very large genus of claimed compositions i.e. a first substance having concentrations ranging from 0.001% to 79.99% and the second substance having concentrations ranging from 20.001% to 99.99% (e.g. 78% alcohol/ 22% DMSO). Therefore the claims, as amended, introduce new matter not disclosed in the specification as originally filed. It is suggested that the claims be amended to claim the invention as recited in the specification as originally filed.

First paragraph of 35 U.S.C. 112: Written Description

5. Claims 1-4, 6-8, 10 and 12-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims, as amended, are

drawn to a composition comprising of a first substance capable of precipitating or denaturing proteins whose concentration is less than 80% of the total composition and a second facilitator substance to aid in the infusion of the first substance whose concentration is greater than 20% of the total composition wherein the concentrations of the first and second substances are effective to stabilize the nucleic acids of said at least one cell in a specimen and wherein the combined concentration of said first and second substances is 100% of the composition. The specification teaches the claimed composition stabilizes vaginal swab samples (page 7, lines 7-9 and 24-26). Additionally, the specification teaches specific cell types found in vaginal fluid i.e. *Trichomonas vaginalis*, *Gardnerella vaginalis* and *Candida albican* and the claimed compositions' stabilization of the structure and nucleic acids in these cell types (pages 11-12, Examples 2 & 4-12). The specification suggests the composition "could be used for other biological specimens" (page 4, lines 26-29). However, the specification does not teach the composition stabilizes the nucleic acids the very large genus of cells in a sample as claimed. The claimed cell in a specimen encompasses eukaryotic cells which further encompasses plant and animal cells each of which further encompass numerous species and sub-species, prokaryotic cells which further encompasses bacteria which further encompasses numerous species not described in the specification. The specification fails to teach a representative number of the claimed species. The specification teaches various formulations of the claimed composition and experimental conditions using the compositions (Examples 4-12) but the specification does not teach using the claimed composition with a representative number of the claimed cell species. Therefore, the specification does not provide a written description of the claimed composition in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The courts have stated that the specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonable conclude the inventor had possession of the claimed invention see *In re Vas-Cath*, Inc. 935F2d. 1555, 1563, 19 USPQ2d 1111,1116.

It is suggested that the claims be amended to claims the invention as described in the specification e.g. by inserting "in vaginal fluid" after "one cell" in line 2 of Claim 1.

Response to Arguments

6. Applicant argues that the specification provides strong support for the claims present in the specification and specifically points to Example 11 to illustrate the support. However, while Example 11 illustrates that a composition consisting of 50%methanol/50% DMSO protects RNA from nuclease digestion, the specification does not provide support for the very large genus of compositions and cell specimens as claimed. Example 11 illustrates that RNA spotted on a dipstick remained visible in the presence of vaginal fluid, whole blood, serum and plasma samples in the presence of a 50% methanol/50% DMSO composition but when the same samples did not contain the composition the RNA was not visible. This clearly illustrates that the composition consisting of 50% methanol/50% DMSO protects extracellular RNA from digestion but this does not illustrate the stabilization of nucleic acids of at least one cell in a specimen nor does this illustrate support for the large genus of compositions claimed. The claimed invention is drawn to compositions encompassing a very large genus of compositions comprising composition concentrations not disclosed in the specification i.e. a first substance having a large genus of concentrations ranging from 0.001% to 79.99% and a second substance having a large genus of concentrations ranging from 20.001% to 99.99% wherein the concentration of the first and second substances are effective to stabilize the nucleic acids of at least one cell in a specimen at ambient temperature. Example 11 illustrates a single species of the large genus of claimed compositions is effective to stabilize extracellular nucleic acids. Therefore, the specification does not provide support for the invention as claimed.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 1, 2, 4, 8 and 13-16 are rejected under 35 U.S.C. 102 (b) as being anticipated by Evinger-Hodges et al. (WO 90/02204, published 8 March 1990) as taught by Gee et al. (U.S.

Patent No. 6,162,931, filed 12 April 1996) and Morris, C. ed. (Academic Press Dictionary of Science and Technology, 1992, page 837).

Regarding Claim 1, Evinger-Hodges et al. disclose a composition for stabilizing the nucleic acids of a cell fixation at ambient temperature (page 6, line 35-page 7, line 2), the composition comprising: an alcohol and a facilitator substance i.e. 50% methanol/50% acetone (page 13, lines 24-35) i.e. the cellular constituents are fixed and the nucleic acids are retained in their appropriate location and nucleic acids are not modified in such a way as to inhibit hybridization (page 13, lines 10-21). Gee et al. teach acetone when added to fixative is a facilitator substance which allows other substances to move across cell membranes (Column 30, lines 54-56) and Morris ed. teach that fixatives preserve and stabilize. Therefore, Evinger-Hodges et al. disclose the claimed composition for stabilizing the nucleic acids of at least one cell.

Regarding Claim 2, Evinger-Hodges et al. disclose the claimed composition wherein said at least one alcohol is methanol (page 13, lines 24-35).

Regarding Claim 4, Evinger-Hodges et al. disclose the claimed composition wherein said first substance is comprised of one alcohol i.e. methanol (page 13, lines 24-35).

Regarding Claim 8, Evinger-Hodges et al. disclose the claimed composition wherein the ratio of the first and second substance is 1:1 i.e. 50% methanol : 50% acetone (page 13, lines 24-35).

Regarding Claim 13, Evinger-Hodges et al. disclose the claimed composition wherein the nucleic acid is DNA (page 6, lines 1-7).

Regarding Claim 14, Evinger-Hodges et al. disclose the claimed composition wherein the nucleic acid is RNA (page 6, lines 1-7).

Regarding Claim 15, Evinger-Hodges et al. disclose the claimed composition wherein said RNA is ribosomal RNA (page 6, lines 1-7).

Regarding Claim 16, Evinger-Hodges et al. disclose the claimed composition wherein cell is a eukaryote (Example 7, page 33, lines 16-22).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 3, 6, 7, 10, 12 & 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gee et al. (U.S. Patent No. 6,162,931, filed 12 April 1996) and Evinger-Hodges et al. (WO 90/02204, published 8 March 1990). The claims are drawn to a composition comprising :a first substance capable of precipitating or denaturing proteins comprising at least one alcohol or ketone whose concentrations is less than 80% of the composition and a second facilitator substance to aid in the infusion of the first substance whose concentration is greater than 20% of the composition. The recitation "are effective to stabilize the nucleic acids of said at least one cell" is an inherent property of the composition comprising the claimed components and are not considered to be further limiting on the composition as claimed.

Regarding Claim 3, Evinger-Hodges et al. teach a composition for stabilizing the nucleic acids of a cell fixation at ambient temperature (page 6, line 35-page 7, line 2), the composition comprising: an alcohol and a facilitator substance i.e. 50% methanol/50% acetone (page 13, lines 24-35) i.e. the cellular constituents are fixed and the nucleic acids are retained in their appropriate location and nucleic acids are not modified in such a way as to inhibit hybridization (page 13, lines 10-21). Gee et al. teach acetone when added to fixative is a

facilitator substance which allows other substances to move across cell membranes (Column 30, lines 54-56) and Morris ed. teach that fixatives preserve and stabilize. Therefore, Evinger-Hodges et al. disclose the claimed composition for stabilizing the nucleic acids of at least one cell. Evinger-Hodges et al. do not teach the second substance is dimethyl sulfoxide (DMSO). However, Gee et al. teach a similar composition comprising; a first substance capable of precipitating or denaturing proteins comprising alcohol i.e. a fixative solution comprising methanol, and a second facilitator substance to aid in the infusion of the first substance into said at least one cell i.e. DMSO, wherein the concentrations of said first and second substances are effective to stabilize the structure and nucleic acids of said at least one cell (Column 30, lines 46-60). The courts have stated that in considering methods, it would be obvious to one of skill in the art in view of the method to "substitute one equivalent for another" and "express suggestion to substitute one equivalent for another need not be present to render such substitution obvious" (see *In re Fout*, 213 USPQ 532). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the acetone facilitator substance in the fixative of Evinger-Hodgers et al. with DMSO based on the teaching of Gee et al. wherein acetone and DMSO function equivalently in a fixative composition to facilitate transmembrane transport.

Regarding Claims 6 and 7, Evinger-Hodges et al. teach the claimed composition wherein said first substance is comprised of one alcohol and they teach the alcohol is ethanol or methanol (page 13, lines 24-35) but they do not teach the first substance is comprised of a first alcohol or ketone and a second alcohol or ketone (Claims 6) wherein the concentrations of the first and second substances is 2.5:2.5:5 (Claim 7). However, the courts have stated with regard to chemical homologs that the greater the physical and chemical similarities between the claimed species and any species disclosed in the prior art, the greater the expectation that the claimed subject matter will function in an equivalent manner (see *Dillon*, 99 F.2d at 696, 16 USPQ2d at 1904). It was known in the art at the time the claimed invention was made that

ethanol and methanol are chemical homologs due their physical and chemical similarities. Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the alcohol composition of Evinger-Hodges et al. based on their ethanol or methanol teaching and using routine experimentation add a second alcohol to the composition to thereby optimized experimental conditions and maximized experimental results for a specific cell type as taught by Evinger-Hodges et al. (page 13, lines 21-23). The skilled practitioner would have been motivated to alter the ratios of the substances in the composition based on the cell and specimen type being stabilized for the obvious benefit of optimizing the composition to thereby maximize stabilization of the nucleic acids for each specific cell and specimen type. It is noted that *In re Aller,* 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation.

Regarding Claim 10, Evinger-Hodges et al. teach the claimed composition wherein said first substance is comprised of one alcohol and they teach the alcohol is ethanol or methanol and they teach the second substance is acetone (page 13, lines 24-35) but they do not teach composition comprises a first alcohol, ethanol, and a second alcohol, methanol and they do not teach the second substance is DMSO. However, Gee et al. teach the similar composition wherein said first substance is methanol and said second substance is DMSO and they teach that DMSO and acetone function to facilitate infusion (Column 30, lines 46-56). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the acetone which facilitates infusion in the fixative composition of Evinger-Hodges et al. with the functional equivalent, DMSO, as suggested by Gee et al. based on available reagents for the expected benefit of convenience. Additionally, it was known in the art at the time the claimed invention was made that ethanol and methanol are chemical homologs due their physical and chemical similarities. The courts have stated with regard to chemical homologs that the greater the physical and chemical similarities between the claimed species

and any species disclosed in the prior art, the greater the expectation that the claimed subject matter will function in an equivalent manner (see *Dillon*, 99 F.2d at 696, 16 USPQ2d at 1904). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the alcohol composition of Evinger-Hodges et al. based on their ethanol or methanol teaching and using routine experimentation add a second alcohol to the composition to thereby optimized experimental conditions and maximized experimental results for a specific cell type as taught by Evinger-Hodges et al. (page 13, lines 21-23).

Regarding Claim 12, Evinger-Hodges et al. teach the composition wherein the first substance is methanol and the second substance is acetone (page 13, lines 29-35) but they do not teach the second substance is DMSO. However, Gee et al. teach the similar composition wherein said first substance is methanol and said second substance is DMSO and they teach that DMSO and acetone function to facilitate infusion (Column 30, lines 46-56). The courts have stated with regard to chemical homologs that the greater the physical and chemical similarities between the claimed species and any species disclosed in the prior art, the greater the expectation that the claimed subject matter will function in an equivalent manner (see *Dillon*, 99 F.2d at 696, 16 USPQ2d at 1904). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the acetone which facilitates infusion in the composition of Evinger-Hodges et al. with the functional equivalent, DMSO, as suggested by Gee et al. based on available reagents for the expected benefit of convenience.

Regarding Claim 17, Evinger-Hodges et al. teach the claimed composition wherein cell is any material which is composed of cells (page 11, lines 30-35) and it was known in the art at the time the claimed invention was made that microorganisms comprises cells i.e. bacterial cells, yeast cells and etc. Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the composition of Evinger-Hodges et

al. to microorganisms for the obvious benefit of stabilizing the nucleic acids of clinically important organisms for study and diagnostic purposes.

Response to Arguments

11. Applicant's arguments have been considered but are deemed moot in view of the withdrawn rejections and new grounds for rejection. However, as they apply to the above rejection, the arguments have been addressed.

Applicant argues that Gee et al. does not disclose stabilizing nucleic acids. The argument is not found persuasive because Gee et al. specifically teach fixing the cell and preserving cellular morphology (Column 30, lines 49-50) and it was known in the art at the time the claimed invention was made that fixation stabilizes cellular constituents for storage of at least 5 months as taught by Evinger-Hodges (page 14, lines 24-31).

Applicant argues that the fixation of Gee et al. is followed by the additional steps of washing and permeabilization. This argument is not found persuasive because Gee et al. specifically teach the fixation is accompanied by permeabilization (Column 30, lines 54-56) and they teach the fixation is optionally followed by washing (Column 30, lines 37-39).

Applicant argues that Gee et al. teach cold methanol and not the claimed ambient temperature. This argument is not found persuasive because Evinger-Hodges teach fixation at ambient temperature (page 6, line 35-page 7, line 2).

Applicant argues that Evinger-Hodges et al. teach the cells of interest are deposited on a solid surface prior to fixation and that they teach the fixatives vary depending on the cell type. In response to applicant's argument that the references show certain features of not recited in applicant's invention, it is noted that the features upon which applicant relies (i.e., deposit of cells on a solid support and fixative relative to cell type) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). This argument is not found persuasive because the instant claims are drawn a composition comprising an alcohol or a ketone and a facilitator and both Gee et al. (Column 30, lines 46-56) and Evinger-Hodges et al. (page 13, lines 29-33) teach a composition comprising an alcohol and a facilitator. The manner in which Evinger-Hodges et al. use the composition is not relevant to the claimed composition.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
August 16, 2001